1191-6 Attenuation of Acetylcholine Mediated Coronary Vasoconstriction With Nonvasodilating Dose of Nitroglycerin in Patients With Heart Failure: Evidence for Nitroglycerin Induced Enhancement of Endogenous Nitric Oxide Effect?

U. Elkayam, A. Mehra, J.Y. Kauffman, H. Gogia, S. Bokhari, P.P. Tummala. *USC School of Medicine, Los Angeles, CA, USA*

It has been suggested that nitroglycerin (N) enhances vasodilating effect of endothelium-derived nitric oxide (NO) on the peripheral vasculature in patients with heart failure (HF). The present study was designed to assess potential interaction between N and NO in the coronary circulation. Effect of intracoronary acetylcholine at doses of 10^{-7}, 10^{-6}, and 10^{-5}M alone (A) and in combination with a small dose (10^{-9}M) of N (A + N) on mean diameter of a proximal (P) and distal (D) segments of an epicardial coronary artery was studied in 11 patients with HF. Results were as follows:

			10^{-7}M		10^{-6}M		10^{-5}M	
	BL	N10^{-9}	A	A + N	A	A + N	A	A + N
P (mm)	3.0	3.1	2.9	3.2†	2.7*	3.2†	2.4*	2.9†
D (mm)	2.1	2.4	1.9	2.5†	1.8	2.2	1.2*	1.6†

BL = baseline; *p < 0.05 vs BL; †p < 0.05 vs A

In addition, reduction of coronary blood flow (CBF) with acetylcholine 10^{-5}M (117 vs 108 ml, p < 0.05) was prevented during concomitant small dose nitroglycerin (126 vs 123 ml, p = NS).

Conclusions: Coronary vasoconstriction and reduction of CBF induced by A are attenuated or prevented with nonvasodilating dose of N. These findings suggest enhancement of endogenous NO effect on the coronary circulation with N in patients with HF.

1191-7 Endothelin Converting Enzyme Inhibition Results in Greater Vasodilation Than ET-A Receptor Blockade in the Forearm of Normal Volunteers

X.-W. Yan, G. Sütsch, C. Schalcher, W. Kiowski. *Division of Cardiology, University Hospital, Zürich, Switzerland*

Background: Endothelin-1 mediates vasoconstriction through two types of receptors (ET-A and ET-B) but the role of the ET-B receptor is unclear.

Methods: We studied forearm vasodilation (plethysmography) during a maximally effective dose of an ET-A receptor antagonist alone (brachial artery infusion of BQ 123, 36 μg/min/100 ml tissue for 25 min) and during randomized, additional endothelin converting enzyme (ECE) inhibition (phosphoramidone (Phosp), 20 μg/mon/100 ml for 15 min, n = 6) or placebo (Pla, n = 6) in normal subjects. The dose of Phosph was based on studies which showed that it completely blocked the vasoconstrictor effects of brachial artery infusions of big endothelin-1 (n = 5).

Results: Forearm blood flow (FBF) increased similarly in both groups after BQ 123 (43 and 39%) over the 45 min observation period. Phosp increased FBF significantly further by an mean of 38% (p < 0.01) while Pla did not lead to significant changes (−6%) during the additional 45 min observation period (mean difference between Phosph and Pla 38%, 95% CI 21 to 55%).

Conclusion: Removal of endothelin-mediated vasoconstrictor tone by effective ECE inhibition results in greater vasodilation than ET-A receptor blockade alone. This finding in normal subjects is compatible with a significant vasoconstrictor effect of endothelin-1 on ET-B receptors the magnitude of which appears to be similar to that mediated by the ET-A receptor.

1191-8 Nitric Oxide-dependent and -independent Mechanisms of Flow-mediated Vasoreactivity

M.J. Mullen, M. Taylor, G. Barba, G. Oakley, J.E. Deanfield, R. MacAllister. *Gt Ormond St Hospital and University College London, London, UK*

Arteries dilate in response to increased blood flow and constrict when flow is reduced. The direct effects of flow are modulated by the endothelium, although the mediators responsible depend on the vessel type. In humans *in vivo*, the response of conduit vessels to changes in blood flow has been used to assess endothelial function. The aim of this study was to investigate the role of nitric oxide (NO) as a mediator of the responses of the radial artery to flow *in vivo*. Using high resolution and pulse wave Doppler ultrasound, arterial diameter and blood flow were continuously measured at rest, during inflation of a distal pneumatic cuff to 300 mmHg for 5 minutes (low flow) and for 3 minutes following its release (high flow due to reactive hyperemia;) in 8 healthy subjects (7 males, mean age 30 ± 3 yrs). The effects of the NO synthase inhibitor, N^Gmonomethyl-L-arginine (L-NMMA; 4 μmol/min by intrabrachial infusion) were compared with norepinephrine (NE; 240 pmol/min). Although blood flow was similar with both drugs, flow-mediated dilatation was abolished by L-NMMA but not by NE or vehicle (see table). In contrast,

Radial diameter	Vehicle	NE	LNMMA
Low flow (%)	−3.9 ± 1.05	−8.06 ± 1.2*	−5.5 ± 1.3
Low flow AUC	−667 ± 207	−1921 ± 351*	−1431 ± 304
High flow (%)	4.2 ± 1.0	1.8 ± 1.4	−0.3 ± 0.8*
High flow AUC	436 ± 163	150 ± 191	−251 ± 102*

Data are expressed as % change from baseline (mean ± SEM); AUC = area under diameter-time curve, *p < 0.05 compared to vehicle

the constriction caused by low-flow was not altered significantly by L-NMMA, but was augmented by NE. These data suggest that flow-mediated dilatation of the radial artery is largely NO-mediated. Constriction of this vessel in response to low flow appears to be independent of NO. The role of endothelial mediators in the mechanism of this constriction remains to be determined.

1191-9 Regulation of Peripheral Vascular Tone in Patients With Heart Failure: Contribution of Angiotensin II

D.E. Newby, N.E.R. Goodfield, A.D. Flapan, N.A. Boon, K.A.A. Fox, D.J. Webb. *University of Edinburgh, Edinburgh, UK*

Background: Plasma concentrations of angiotensin II, a potent vasoconstrictor peptide, are increased in patients with heart failure. Recently, losartan, a selective angiotensin II type 1 receptor antagonist, has become available for clinical investigational studies. The aims of the study were to determine the contribution of angiotensin II to basal and sympathetically stimulated arteriolar tone in patients with heart failure.

Methods: Using forearm plethysmography combined with local intra-arterial administration of losartan, we examined the contribution of endogenous angiotensin II to the maintenance of basal and sympathetically stimulated peripheral arteriolar tone in patients with moderate heart failure and matched healthy controls.

Results: Basal forearm blood flows did not differ between patients and controls. Losartan did not affect basal forearm blood flow (95% CI: −5.5 to +7.3%) or sympathetically stimulated vasoconstriction in controls. However, in patients, blood flow increased by 13 ± 5% and 26 ± 7% in response to 30 and 90 μ g/min of losartan respectively (p < 0.001). Lower body negative pressure caused a reduction in forearm blood flow of 20 ± 5% in controls (p = 0.008) and 13 ± 5% (p = 0.08) in patients (p = 0.007; controls *vs* patients). Responses to angiotensin II and norepinephrine did not differ between patients and controls.

Conclusions: Losartan directly causes acute local peripheral arteriolar vasodilatation in patients with heart failure but not healthy control subjects. It would, therefore, appear that endogenous angiotensin II contributes to basal peripheral arteriolar tone in patients with heart failure but does not augment sympathetically stimulated peripheral vascular tone in either group.

1191-10 Nitric Oxide Activity in Arterial and Venous Bypass Grafts

A. Prasad, G. Zalos, R. Mincemoyer, W.H. Schenke, A.A. Quyyumi. *NHLBI, NIH, Bethesda, MD, USA*

We hypothesized that improved survival of internal mammary artery (IMA) conduits compared to saphenous vein grafts (SVG) may be due to preserved endothelial nitric oxide (NO) activity in arterial grafts. For this purpose, we studied endothelium-dependent and -independent dilator and constrictor functions in IMA (N = 6), SVG (N = 25), and native atherosclerotic vessels (NAV) (N = 30) in 30 patients with previous bypass surgery. The epicardial coronary responses to acetylcholine (ACH, 10^{-6}M), L-NMMA (240 μmol), phenylepherine (PE, 64 μg) and sodium nitroprusside (SNP, 60 μg) were measured (Table). IMA had greater NO activity at rest and with stimulation (dilated with ACH, constricted with L-NMMA), compared to SVG and NAV (no significant change). However, the lack of constriction with L-NMMA in SVG and NAV was not due to reduced sensitivity to constrictor agents, because PE produced constriction in both types of vessels. NAV were more sensitive to the NO donor SNP compared to venous or arterial conduits. The age of SVG did not correlate with the degree of response to any agent. In conclusion, IMA have greater NO activity compared to SVG and NAV which may account for their improved long-term survival free of atherosclerosis.

% change in diameters.

	ACH	L-NMMA	PE	SNP
NAV	−3 ± 2	−3 ± 2	−12 ± 7**	15 ± 3**
SVG	−1 ± 2	−1 ± 1	−6 ± 1**	5 ± 1**
IMA	4 ± 2*	−7 ± 1*	−12 ± 1**	1 ± 5

Mean ± SEM, * = P < 0.05, ** = P < 0.01